Original

Nuclear Medicine Review 2005
Vol. 8, No. 2, pp. 100–104

ISSN 1506–9680

VIA MEDICA

Bone turnover markers and bone scintigraphy in the evaluation of skeletal metastases

Beata E. Chrapko, Anna Nocuń, Renata Gołębiewska, Helena Jankowska, Janina Zaorska-Rajca

Chair and Department of Nuclear Medicine, Skubiszewski Medical University of Lublin, Poland

[Received 9 XII 2004; Accepted 22 VIII 205]

Abstract

BACKGROUND: The aim of this study was evaluation of the clinical usefulness of bone scintigraphy and of serum bone turnover marker levels in the assessment of skeletal metastases.
MATERIAL AND METHODS: We investigated 60 patients with suspected skeletal metastases. Serum level of bone-formation marker: amino- terminal propeptide of type I procollagen (PINP) and a bone-degradation marker: carboxy-terminal telopeptide of type I collagen (ICTP) were assessed with radioimmunoassays. Bone MDP-99m-Tc scans were performed as well.
RESULTS: Hot spots were showed in 72% of patients. According to bone scintigraphy the patients were divided in to 3 groups: Group I — without hot spots (n = 16; 26%), Group II up to 10 hot spots (n = 25; 42%) and Group III more that 10 hot spots (n = 19; 32%). Mean serum level of ICTP was significantly higher in Group II than in Group I ($p < 0.05$), as well as in Group III compared to Group II ($p < 0.001$) and in Group III compared to Group I ($p < 0.001$). There is only one significant relationship in PINP levels — between Groups II and III.
CONCLUSIONS: The levels of bone pathological degradation (ICTP) and bone formation reflect the metastatic disease extent in bone. Serum ICTP level is more useful in staging metastasis. Significantly higher PINP reflects only a much disseminated process.
Key words: bone scintigraphy, skeletal metastases, bone turnover markers

Correspondence to: Beata E. Chrapko
Chair and Department of Nuclear Medicine
Skubiszewski Medical University of Lublin
Jaczewskiego 8, 20–090 Lublin, Poland
Tel/fax: (+48 81) 724 43 39
e-mail: beachra@o2.pl

Introduction

Metastases to the osseous system result from the advancement of such neoplasms as: prostate cancer, lung cancer, breast cancer, thyroid gland or renal cancer. The factors that influence the development of metastases include: the degree of cancer malignancy, its histological type, the formation of emboli from cancerous cells in blood vessels and cancerous infiltrations in bone marrow [1].

The complications which result from metastases to bones are: hypercalcaemia, pain and pathological fractures — especially dangerous in the case of changes in the spinal column because of the possibility of pressure on the spinal cord. The destruction of bones in metastatic disease is linked with the process of osteoclastic activation. The process of the formation of metastases is a multi-stage phenomenon which includes: the destruction of the tissue surrounding a tumour by cancerous cells, the invasion of cancerous cells into the lumen of blood vessels and their transport to the places of metastasis formation, the adhesion of the cells to the endothelium and their infiltration through the wall of a blood vessel as well as the invasion of destination tissue.

According to current knowledge, the pathological changes in structure and function of bones, which are invaded by cancerous cells, result mainly from the disturbances in activities between osteoclasts and osteoblasts and, to a lesser extent, from direct infiltration by cancerous cells.

In patients with suspicion of metastatic disease due to the character of primary neoplasm, diagnostic tests, which aim to determine whether there are metastases to the osseous system and if so, to determine the extent to which the osseous system is affected, prove invaluable.

The marker of bone turnover of which the level in blood plasma reflects the degree of cancer dissemination in bones is

C-terminal telopeptide of type I collagen (ICTP), the product of degradation of type I collagen [2, 3]. There exist two means of osseous resorption: the first, activated by cathepsin-K, is characteristic of physiological reconstruction, and the other, activated by metalproteinases of extracellular space (MMP), is characteristic of cancerous destruction of bones. The level of ICTP reflects the destruction of osseous collagen, which takes place by means of MMP, and it does not show any growth in the case of physiological reconstruction, for instance in postmenopausal osteoporosis [4].

The blood plasma level of N-terminal propeptide of type I procollagen (PINP) is an indicator of the formation of new osseous collagen fibres (Type I), the monitoring of its concentration can consequently be used to determine the level of bone turnover in various diseases, also in skeletal metastatic disease [3, 5].

Bone scintigraphy, as well as the above-mentioned markers, reflects metabolic changes in bones. This is the simplest nuclear medicine method used in the evaluation of patients with cancer and suspicion of bone metastases [6]. This technique is very sensitive because changes in calcification of 5–10% in local metabolism are easily detected. The accumulation of osteotropic tracers used in bone scintigraphy depends on the blood supply in bones, the content of collagen, mineralization, the activity of bone reconstruction and hormonal factors. Osteotropic tracers accumulate via chemoabsorption into forming crystals of hydroxyapatite in their immature form, i.e. in the places of active mineralization of freshly produced osteoid by osteoblasts [7]. This fact was confirmed by Einhorn's histological tests, which showed the accumulation of osteotropic complexes with 99m-Tc in calcification fronts [8]. Metastatic changes in bone scintigraphy can be shown, on average, 12 months earlier than in classic X-ray images. Bone scintigraphy is characterized by high sensitivity — 97%. Firstly, metastases stimulate metabolic processes in adjacent osseous tissue, and then they cause changes in the structure [9].

The aim of this study was to evaluate the clinical usefulness of bone scintigraphy and serum bone turnover marker levels in the assessment of skeletal metastases.

Material and methods

The study was performed on 60 patients (29 women and 31 men) aged from 33 to 75 years (the mean age was 60 years). All the patients had been diagnosed with cancer and referred for bone scintigraphy with suspicion of skeletal metastases. The studied group included 20 cases of breast cancer, 20 patients with prostate cancer and 20 cases of other malignancies like pulmonary cancer and kidney cancer (Table 1). Twenty healthy volunteers ranging in age from 30 to 57 years (mean age 50 years) were studied as the control group (CG) with respect to bone turnover markers.

Whole body scans were performed on all the patients, using the "step and shoot" method (4 minutes per image), 2.5 hours after intravenous injection of MDP-99mTc. The examinations were performed utilising a dual-head gamma camera Varicam (Elscint, Haifa, Israel). Acquisition was performed using 256 × 256 matrix and high-resolution collimator (VPC 45). Additional projections were performed in the majority of cases. On the day of scintigraphic imaging, serum levels of UniQ ICTP and UniQ PINP (Orion Diagnostica, Espoo, Finland) were measured in all the patients, using the RIA method. The normal range of serum ICTP and PINP was respectively: for female 1.6 μg/L — 5.0 μg/L and 20.0 μg/L — 76.0 μg/L, for male 1.3 μg/L — 5.2 μg/L and 19.0 μg/L — 84.0 μg/L. Based on scintigraphic findings (SF), the patients were divided into three groups: Group I — with no "hot" spots, typical for osteoblastic metastases (16 patients — 26%), Group II — with less than 10 "hot" spots (25 patients — 42%), Group III with more than 10 " hot" spots (19 patients — 32%) (Table 2).

Table 1. Prevalence of breast cancer and prostate cancer in the studied groups of patients

Type of cancer	Whole Group n	Group I n	Group II n	Group III n
Breast cancer	20	6	8	6
Prostate cancer	20	6	11	3
Other malignancies	20	4	7	10

Table 2. The groups of the patients according to scintigraphic findings

Group	n (%)	Age X ± SD	Number of hot spots
I	16 (26%)	56 ± 12	None
II	25 (42%)	62 ± 9.6	Less than 10
III	19 (32%)	61 ± 8.8	More than 10

Results

"Hot" spots, characteristic for bone metastases, were detected in bone scans in 72% of the patients (Figure 1). Table 3 shows the levels of the tested markers. In the whole group of patients who were examined, the concentration of PINP was 86.66 ± 175.25 μg/l, that of ICTP was 6.56 ± 5.94 μg/l, in the control group the concentration of PINP was 40.0 ± 11.0 μg/l and that of ICTP — 2.5 ± ± 0.9 μg/l.

In analyzing the whole group of patients (Table 4) statistically significant correlations between PINP and ICTP were detected ($r = 0.661$, $p < 0.001$) as well as between PINP and the number of hot foci ($r = 0.641$; $p < 0.001$) and also between ICTP and the number of metastatic changes ($r = 0.536$; $p < 0.001$). No significant relationship between the tested markers of bone turnover and the age of the patients was determined.

As far as the analysis based on the division into groups is concerned (Table 5), no statistically significant differences in levels of PINP and ICTP between Group I and the control group were shown. Statistically significant differences in concentrations of ICTP were shown between Group I and II ($p < 0.05$), between Groups I and III ($p < 0.001$) and between Groups II and III ($p < 0.001$). The only statistically significant difference in the concentration of PINP was present between Group II and Group III ($p < 0.05$).

In Group I, the prevalence of elevated ICTP concentration was 6.25%. This figure increased to 32.0% in Group II and 87.5% in Group III. The prevalence of elevated PINP in Groups I–III was respectively: 18.75%, 8.0%, 44.0%. In the control group, no elevated ICTP or PINP results were observed.

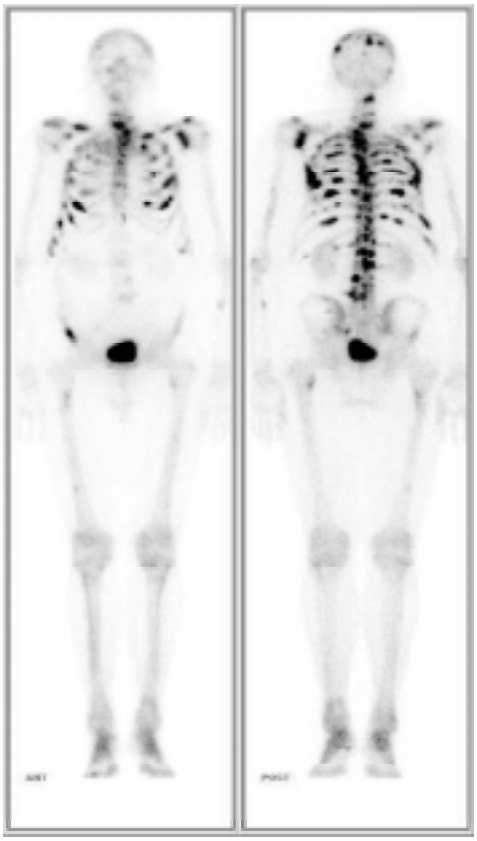

Figure 1. MDP99mTc bone scan of a 64-year-old patient with multiple osteosclerotic metastases from prostate cancer.

Discussion

Numerous studies show that skeletal scintigraphy with MDP-99mTc is an excellent tool for early detection of metastatic changes as well as for monitoring the course of a disease, especially in the case of breast and prostate cancer. Skeletal scintigraphy is highly sensitive and in skilled hands it can also be highly specific with respect to these diseases [10]. Crippa et al. demonstrated, on the basis of 1971 bone scans carried out in 260 women patients diagnosed with breast cancer and monitored for 10 years, the sensitivity of this test to be about 98.2% and specificity 95.2%, accuracy 95.5%, positive predictive value 72.8% and negative predictive value 99.8% [11]. Cereceda et al, who dealt with a problem of metastatic changes of the spinal column in patients with prostate cancer, state that skeletal scintigraphy is the most effective screening method in these patients [12].

There are methods of semi-quantitative skeletal scintigraphy evaluation in patients with metastatic changes in bones; however, one of the better-known methods is evaluation according to Soloway [13]. According to this division, the first degree of the advancement in metastatic process corresponds in skeletal scintigraphy to the presence of fewer than six changes, each of which corresponds to about 50% of the size of vertebra. The second degree corresponds to the number of changes from 6 to 20; the third degree means more than 20 changes but not superscan, the fourth degree- "superscan" — corresponds to the situation in which over 75% of ribs, spinal column and pelvic bones are affected. This division, according to the authors of this paper is rather appropriate for the group with a more advanced metastatic process than the group presented in this paper. Another classification was used by Konieczna et al [14]: the classification in which a group without any metastases was taken into account (Group O), as well as a group with single metastases (Group I) and group with multiple metastases (Group II).

In this paper we used our own, somehow modified division of patients, which depends on the number of "hot" spots detected in skeletal scintigraphy. Group I without "hot" foci typical of osteoblastic metastases, Group II with up to 10 "hot" spots, and Group III with more than 10 "hot" foci.

Skeletal scintigraphy is one of the most frequently carried out isotopic examinations, and the main question put by clinicians to nuclear medicine specialists is whether patients diagnosed with cancerous processes have metastatic changes in bones or not. Fairly frequently this is a difficult question to answer as a result of

Table 4. Correlations between measured parameters in the whole group of patients

Correlation	p
PINP *vs.* ICTP	< 0.001
PINP *vs.* SF	< 0.001
PINP *vs.* age	> 0.05
ICTP *vs.* SF	< 0.001
ICTP *vs.* age	< 0.002

PINP — Procollagen IN-terminal peptide; ICTP — I Collagen C-telopeptide

Table 5. Comparison between PINP and ICTP in the studied groups

Comparison of the groups	PINP	ICTP
I *vs.* control group	NS	NS
I *vs.* II	NS	$p < 0.05$
I *vs.* III	NS	$p < 0.001$
II *vs.* III	$p < 0.05$	$p < 0.001$

PINP — Procollagen IN-terminal peptide; ICTP — I Collagen C-telopeptide; NS — non significant

Table 3. Serum levels of examined markers

Serum level [μg/l]	Control group	Whole group	I	II	III
PINP X ± SD	**40.0** ± 11	**86.6** ± 175.3	**53.5** ± 21.3	**42.4** ± 19.4	**188.9** ± 313.1
ICTP X ± SD	**2.5** ± 0.9	**6.6** ± 5.94	**3.4** ± 1.9	**4.9** ± 2.2	**12.3** ± 8.3

PINP — Procollagen IN-terminal peptide; ICTP — I Collagen C-telopeptide

the coexistence of posttraumatic or degenerative changes, especially in elderly people. The test of bone turnover markers is an additional, auxiliary test carried out by many hospitals in order to evaluate the progression of metastatic processes and to monitor their development [6, 7, 15, 16].

Some authors propose determining the levels of PINP and ICTP for a screening test qualifying for skeletal scintigraphy [14]. These authors suggest that the lack of deviation from the normal levels of the determined bone turnover markers allows skeletal scintigraphy not to be carried out since such a result rules out, to a high probability, the existence of metastases to the osseous system. The authors of the currently presented paper accord with this statement because in the group of patients examined by us without any metastatic changes in scintigraphy, the values of both PINP and ICTP did not differ in comparison with control groups. Tahtela et al [3] point out that the determination of concentration of bone turnover markers (ICTP, PINP and PICP) solely is not sensitive enough for full diagnosis; however, these tracers can be helpful in diagnosing and monitoring metastatic disease of bones. Schoenberger et al [17] underlines that PINP and ICTP are less expensive than bone scans, but the sensitivity and specificity of these markers for the detection of bone metastases are low. For that reason, PINP and ICTP cannot be used as screening parameters in metastatic bone disease. Ebert et al. concluded that in patients with lung cancer, the currently available bone markers (among others — PINP and ICTP) cannot replace bone scintigraphy either for screening or for monitoring bone metastases [18].

Similarly to other authors [19], in this paper, we demonstrate a significant relationship between the degree of advancement in metastatic processes detected in skeletal scintigraphy and the values of bone turnover markers. What is more, Konieczna et al [14] points out the best correlation of PINP with scintigraphic changes, whereas in the material tested by us, both ICTP and PINP show the same degree of correlation with scintigraphic image with regard to the whole group of patients.

Koizumi et al [20] demonstrated the values of ICTP determinations in skeletal metastatic disease and they highlighted the lack of this tracer elevation in the menopausal period. The authors of this article obtained similar results, where no relationship between osseous turnover tracers and age was established and ICTP was a better marker for determining the current advancement in skeletal changes.

Some authors emphasize a predictive value of both markers — ICTP and PINP, in evaluating cancer patients. Jukkola et al. have found the recurrence of the disease in 32% of 373 cases of node-positive breast cancer during 45 months after surgical treatment. Serum level of PINP was significantly higher in patients with bone metastases than without. These authors suggest that the high level of PINP in these patients during the postoperative period is an indicator of unfavourable prognosis [21]. According to Ylisirnio et al, elevated levels of ICTP and CrossLaps in lung cancer patients predict a shorter duration of survival [22]. Simojoki et al estimated the predictive value of bone turnover markers in patients with epithelial ovarian cancer. In these patients, a high level of ICTP and low ratio of carboxyterminal propeptide of type I procollagen (PICP) to aminoterminal (PINP) — PICP: PINP, are prognostically unfavourable [23].

Studies of Kobayashi et al [24] pointed out that the measurement of serum PINP and ICTP is useful not only in detecting the progression of cancer but also in serial monitoring of metastases, including assessment of therapeutic response.

Unfortunately, serial monitoring of our patients was not possible — the measurement of bone turnover markers and skeletal scintigraphy were performed only once. Therefore, based on acquired data, we cannot draw broader conclusions than those presented below.

Conclusions

A significant correlation exists between the level of bone turnover markers PINP and ICTP and the degree of advancement of skeletal metastatic processes evaluated by means of scintigraphy.

The concentration of Type I collagen molecule degradation marker ICTP allows a more precise determination of the degree of advancement of this process than the level of PINP, the marker of bone formation.

A significant increase in PINP value is present only in the case of multiple metastatic changes in bones.

Bone scintigraphy with bone turnover markers, especially ICTP, can help in better assessment and in monitoring of metastatic bone disease.

References

1. Stajszczyk M, Mykała-Cieśla J. Bisphosphonates in the treatment of breast carcinoma. Pol Arch Int Med 2001; 2: 729–738.
2. Koizumi M, Ogata E. Bone metabolic markers as gauges of metastasis to bone: review. Ann Nucl Med 2002; 16: 161–168.
3. Tahtela R, Tholix E. Serum concentration of type I collagen carboxyterminal telopeptide (ICTP) and type I procollagen carboxy-and aminoterminal propeptides (PICP, PINP) as markers of metastatic bone disease in breast cancer. Anticancer Res 1996; 16: 2289–2293.
4. Noguchi M, Noda S. Piridinoline cross-linked carboxyterminal telopeptide of type I collagen as a useful marker for monitoring metastatic bone activity in men with prostate cancer. J Urol 2001; 166: 1106––1111.
5. Koizumi M, Yonese J, Fukui I, Ogata E. The serum level of aminoterminal propeptide of type I procollagen am a sensitive marker for prostate cancer metastasis to bone. BJU Int 2001; 87: 348–351.
6. Buscombe JR, Holloway B, Roche N, Bombardieri E. Position of nuclear medicine modalities in the diagnostic work-up of breast cancer. Q J Nucl Med Mol Imaging 2004; 48: 109–118.
7. Bombardieri E, Aktolun C, Baum RP et al. Bone scintigraphy: procedure guidelines for tumor imaging. Eur J Nucl Med Mol Imag 2003; 30: BP99–BP106.
8. Einthorn TA, Vigorita VJ, Aaron A. Localization of technetium-99m methylene diphosphonate in bone using microradiography. J Orthop Res 1986; 4: 180–187.
9. Van der Wall H. The evaluation of malignancy: metastatic bone disease. Murray IPC, Ell PJ (eds). Nuclear Medicine in clinical diagnosis and treatment. Churchill Livingstone, Edinburgh 1994: 949–962.
10. Maffioli L, Florimonte L, Pagani L, Butti I, Roca I. Current role of bone scan with phosphonates in the follow-up of breast cancer. Eur J Nucl Med Mol Imag 2004; 31 (Suppl 1): 143–148.
11. Crippa F, Seregni E, Agresti R, Bombardieri E, Buraggi GL. Bone scintigraphy in breast cancer: ten years follow up study. J Nucl Biol Med 1993; 37: 57–61.
12. Cereceda LE, Flechon A, Droz JP. Management of vertebral metastases in prostate cancer: a retrospective analysis in 119 patients. Clin Prostate Cancer 2003; 2: 34–40.

13. Soloway MS, Hardeman SW, Hickey D et al. Stratification of patients with metastatic prostate cancer based on extend of disease on initial bone scan. Cancer 1988; 61: 195–202.
14. Konieczna M, Pietrzykowski J, Chmielowski K, Dziuk E. The possibility of qualification patients suspected of bone metastases for skeletal scintigraphy according to concentration of collagen turnover markers. Nucl Med Rev Cent East Eur 2002; 1: 73.
15. Berruti A, Dogliotti L, Gorzegno G et al. Differential patterns of bone turnover in relation to bone pain and disease extent in bone in cancer patients with skeletal metastases. Clin Chem 1999; 45: 1240–1247.
16. Luftner D, Richter A, Geppert R, Wernecke KD, Possinger K. Normalization of biochemical markers of bone formation correlates with clinical benefit from therapy in metastatic breast cancer. Anticancer Res 2003; 23: 1017–1026.
17. Schoenberger J, Rozeboom S, Wirthgen-Bever E, Eilles C. Evaluation of the clinical value of bone metabolic parameters for the screening of osseous metastases compared to bone scintigraphy. BMC Nucl Med 2004; 4: 3.
18. Ebert W, Muley T, Herb KP, Schmidt-Gayk H. Comparison of bone scintigraphy with bone markers in diagnosis of bone metastasis in lung carcinoma patients. Anticancer Res 2004; 24: 3193–3201.
19. Noguchi M, Yahara J, Noda S. Serum level of bone turnover marker parallel the results of bone scintigraphy in monitoring bone activity of prostate cancer. Urology 2003; 61: 993–998.
20. Koizumi M, Takahashi S, Ogata E. Comparison of serum bone resorption markers in the diagnosis of skeletal metastasis. Anticancer Res 2003; 23: 4095–4099.
21. Jukkola A, Bloigu R, Holli K and al. Postoperative PINP in serum reflects metastatic potential and poor survival in node-positive breast cancer. Anticancer Res 2001; 21: 2873–2876.
22. Ylisirnio S, Sassi ML, Risteli J, Turpeenniemi-Hujanen T, Jukkola A. Serum type I collagen degradation markers, ICTP and CrossLaps, are factors for poor survival in lung cancer. Anticancer Res 1999; 19: 5577––5581.
23. Simojoki M, Santala M, Risteli J, Kauppila A. Discrepant expression of carboxy- and aminoterminal propeptides of type I procollagen predicts poor clinical outcome in epithelial ovarian cancer. Gynecol Oncol 2003; 88: 358–362.
24. Kobayashi T, Gabazza EC, Taguchi O et al. Type I collagen metabolites as tumor markers in patients with lung carcinoma. Cancer 1999; 85: 1951–1957.